

# Endocrine Late Effects of Childhood Cancer Therapy: A Report from the Children's Oncology Group

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## Key Words

Endocrine late effects • Childhood cancer • Chemotherapy • Radiation therapy • Pediatrics

## Abstract

Pediatric oncologists are curing increasing numbers of patients with childhood cancer, and most children diagnosed with a malignancy may now be expected to become long-term survivors. As the number of childhood cancer survivors grows, so too does the need for evidence-based surveillance of the long-term effects of cancer therapy. Long-term effects involving the endocrine system represent a frequent complication of therapy. The *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG LTFUG)*, most recently updated in 2006, provide a summary of the known endocrine late effects of surgery, radiation, chemotherapy, and stem cell transplant. This paper summarizes the scope and nature of the endocrine late effects of childhood cancer therapy based upon a review of the pertinent medical literature, and demonstrates how pediatric oncologists can use these guidelines in clinical practice.

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## Introduction

One of the most significant advances of modern medicine has been the ability to treat childhood cancer effectively. Pediatric oncologists are curing increasing numbers of children, and today most children diagnosed with a malignancy are expected to become long-term cancer survivors. The 5-year cure rate for childhood cancer is now nearly 80% [1], and for some cancers, such as acute lymphoblastic leukemia and Hodgkin's disease, cure rates exceed 90% [2, 3]. As the number of childhood cancer survivors grows, so too does the need for evidence-based surveillance of the long-term effects of cancer therapy. Nearly two-thirds of all of childhood cancer survivors will suffer some late effect, and the endocrine system is commonly involved [4, 5]. Care of the childhood cancer survivor is shifting from merely the detection of relapse to an improved understanding of the long-term sequelae of cancer treatment.

Because of the continued refinement of childhood cancer therapy, the study of late effects is an ongoing process. New agents, varying doses, and treatment schedules are frequently being developed and tested through national therapeutic protocols. Therefore, the scope of cancer late effects is likely to continue to change over time.

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**Table 1.** Categories of consensus scoring for the COG long-term follow-up guidelines

Cate- gory	Statement of consensus
1	There is uniform consensus of the panel that: (1) there is high-level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members
2A	There is uniform consensus of the panel that (1) there is lower-level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members
2B	There is non-uniform consensus of the panel that (1) there is lower-level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members
3	There is major disagreement that the recommendation is appropriate
<p><i>Uniform consensus:</i> Near-unanimous agreement of the panel with some possible neutral positions.</p> <p><i>Non-uniform consensus:</i> The majority of panel members agree with the recommendation; however, there is recognition among panel members that, given the quality of evidence, clinicians may choose to adopt different approaches.</p> <p><i>High-level evidence:</i> Evidence derived from high-quality case control or cohort studies.</p> <p><i>Lower-level evidence:</i> Evidence derived from non-analytic studies, case reports, case series, and clinical experience.</p>	

As many as 40% of childhood cancer survivors may have endocrine disturbances related to their underlying malignancy, surgery, radiation therapy (RT), or chemotherapy [4, 6]. These factors are further modified by the age at which treatment was initiated, the length of time since treatment, and gender [3, 7]. Many cancer centers have comprehensive, long-term follow-up clinics where interdisciplinary teams screen for late effects based upon published guidelines [8]. These clinics are frequently a source of referrals to pediatric endocrinologists. Given the rising survivorship rates and increasing prevalence of endocrine late effects, pediatric endocrinologists must be prepared to see childhood cancer survivors. The field of endocrine-related late effects is growing and producing a burgeoning body of research, with which pediatric endocrinologists should become familiar.

The purpose of this mini review is to provide an overview of the scope and nature of the endocrine late effects of childhood cancer therapy. We will outline the screening currently recommended by the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG LTFUG)* and provide a summary of the known endocrine late effects of RT, chemotherapy, and hematopoietic cell transplant (HCT). Additionally, we will demonstrate how oncologists approach the detection of late effects and the point at which endocrinology consultation is recommended.

### COG Long-Term Follow-Up Guidelines

The *COG LTFUG* offer guidance for clinical screening for a wide array of late effects that can result from the therapies used to treat pediatric malignancies. The *COG LTFUG* are agent/modality-specific, and subdivided into the following categories: chemotherapy, RT, surgery, HCT, and cancer screening. Initial review of the published medical literature resulted in the development of the first version of the *COG LTFUG* [9]. Before release, the *COG LTFUG* were extensively reviewed and scored by a panel of experts using a modified version of the National Comprehensive Cancer Network 'Categories of Consensus' system (table 1). Each score reflects the strength of data from the literature linking a specific late effect with a therapeutic exposure, coupled with an assessment of the appropriateness of the screening recommendation based on the collective experience of the expert panel, matching the magnitude of the risk of developing the complication with the intensity of the recommended screening. Multidisciplinary system-based task forces organized within the COG Late Effects Committee are responsible for monitoring the literature, evaluating guideline content, and providing recommendations for guideline revision as new information becomes available. The Guidelines Task Force on Endocrine and Metabolic Complications includes 5 pediatric endocrinologists, 3 pediatric oncologists, 1 pediatric radiation oncologist, 1 primary care physician, 3 pediatric oncology nurses, and 1 patient advocate. Task force recommendations for guideline revisions are presented to the Late Effects Steering Committee for approval and scoring before incorporation into the *COG LTFUG*. *Version 2.0*, the most recent update of the *COG LTFUG* and accompanying health education materials are available at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org).

**Table 2.** Endocrine late effects of childhood cancer therapy: COG LTFUG

	GH defi- ciency	Hypo- thyroid- ism	Hyper- thyroid- ism	Thyroid nodule/ cancer	Central adrenal insufficiency	Precoc- ious puberty	Hypo- gonad- ism	Infer- tility	Low bone mineral density	Obesity/ hyper- lipidemia	Metab- olic syn- drome	Hyper prolac- tinemia
Cranial irradiation <sup>1</sup>	+	+		+	+	+	+	+		+	+	+
Total body irradiation	+	+		+			+	+			+	
Target organ irradiation												
Thyroid <sup>2</sup>		+	+	+								
Gonadal <sup>3</sup>							+	+				
Alkylating agents												
Non-classical							+	+				
Alkylators							+	+				
Anthracyclines												
Heavy metals							+	+		+ Dys- lipidemia		
Antimetabolites									+			
Antitumor antibiotics												
Corticosteroids									+			
Enzymes												
Plant alkaloids												
Epipodophyllotoxins												
Hematopoietic cell transplantation									+			

<sup>1</sup> Cranial irradiation includes: cranial, orbital/eye, ear/infratemporal and nasopharyngeal.

<sup>2</sup> Thyroid irradiation includes: thyroid, neck, cervical spine, oropharyngeal, supraclavicular, mantle and mini mantle.

<sup>3</sup> Gonadal radiation includes: lumbosacral spine, abdomen and pelvis (females) and pelvis and testicular (males).

### Using the COG Long-Term Follow-Up Guidelines

The *COG LTFUG* are intended to be used to evaluate patients who have survived at least 2 years beyond the date of completion of cancer therapy. To organize the appropriate risk-based evaluation, a medical summary should be created that includes information about the cancer histology, involved anatomic sites and all therapeutic agents/modalities received with cumulative doses of agents as appropriate. Using the *COG LTFUG*, this information is then used to identify the potential late effects for which the patient may be at risk (table 2). The *COG LTFUG* make recommendations for elements of the history and physical examination, laboratory and imaging studies that should be done to monitor for late effects and the frequency of such evaluations (table 3). Forty-two ‘Health Links’ are also available on the website that can be used to educate families and patients about specific late effects (table 4).

### Cranial Radiation

The impact of RT depends upon the involved field, total dose, and schedule [10]. There is a well-established association between the total radiation dose and the development of pituitary hormone deficiencies [11, 12]. The growth hormone (GH) axis is the most sensitive of the hypothalamic functions to radiation and can be affected at doses of 18 Gy irradiation [13–15]. At hypothalamic doses of radiation >40 Gy, gonadotropin, corticotropin, and thyrotropin secretion may be compromised.

The age of the patient at the time of RT may affect the degree of hypothalamic-pituitary damage sustained. Some studies suggest that younger age at the time of diagnosis and treatment may lead to more deleterious effects on the hypothalamic-pituitary axis [10]. When a child who has undergone cranial RT presents for care, issues of growth, central hypothyroidism, central adrenal insufficiency, precocious puberty, gonadotropin deficiency, hyperprolactinemia, and obesity must all be considered.

**Table 3.** Proposed screening and monitoring for potential late effects based on the COG LTFUG, version 2

Potential late effect	History	History frequency	Physical	Physical frequency	Laboratory studies	Laboratory frequency	Further considerations when to refer
Growth problems	Assess nutritional status	Every 6 months	Height and weight BMI Tanner staging	Every 6 months until growth complete Every 6 months until sexually mature			If poorly growing – bone age and thyroid labs Refer to endocrine if Height <3rd percentile Drop >2 percentile channels Growth <4–5 cm/year Lack of pubertal growth spurt If GH deficiency consider DEXA
Hypothyroidism central and primary	Fatigue, weight gain, cold intolerance, constipation, dry skin, brittle hair, depressed mood	Yearly	Height and weight Hair, skin Thyroid exam	Yearly	Free T <sub>4</sub> TSH	Yearly	Refer to endocrine for thyroid hormone replacement
Hyperthyroidism	Heat intolerance, tachycardia Palpitations, weight loss Emotional lability Muscular weakness Hyperphagia	Yearly	Eyes, skin, Thyroid Cardiac Neurologic	Yearly	Free T <sub>4</sub> TSH	Yearly	Refer to endocrine for management of hyperthyroidism
Thyroid nodule			Thyroid exam	Yearly			Ultrasound and FNA for nodule Refer to endocrine and surgery for biopsy and or thyroidectomy Nuclear medicine for ablation Refer to endocrine for postop. management
Central adrenal insufficiency	Failure to thrive, anorexia Dehydration, hypoglycemia Lethargy unexplained hypotension	Yearly			08:00 a.m. Cortisol	Yearly for 15 years	Refer to endocrine for replacement
Precocious puberty			Height and weight Tanner stage Testicular volume	Yearly until sexually mature	FSH LH Testosterone/ Estradiol	prn signs of early puberty	If rapidly growing – bone age Refer to endocrine if accelerated puberty in girls <8 years old boys <9 years old
Gonadotropin deficiency Delayed puberty Premature menopause Infertility Females	Pubertal (onset, tempo) Menstrual/pregnancy history Sexual function (vaginal dryness, libido) Medication use impacting sexual function	Yearly	Tanner stage	Yearly until sexually mature	FSH LH Estradiol	Begin @ 13 and prn	Consider DEXA Refer to endocrine if Delayed puberty Persistently abnormal labs Refer to reproductive endocrine for Infertility
Gonadotropin deficiency Delayed puberty Infertility Males	Pubertal (onset, tempo) Sexual function (erections, nocturnal emissions, libido) Medication use impacting sexual function	Yearly	Tanner stage Testicular volume	Yearly until sexually mature	FSH LH Testosterone	Begin @ 14 and prn  prn	Consider DEXA Refer to endocrine if Delayed or arrested puberty Persistently abnormal labs Refer to reproductive endocrine for infertility consider inhibin B
Hyperprolactinemia	Galactorrhea Decreased libido (males) Menstrual history (females)	Yearly			Prolactin	prn	Consider CT of the sella Refer to endocrine if hyperprolactinemia, galactorrhea or amenorrhea

**Table 3** (continued)

Potential late effect	History	History frequency	Physical	Physical frequency	Laboratory studies	Laboratory frequency	Further considerations when to refer
Low bone mineral density					Bone density evaluation DEXA or quantitative CT	Baseline <sup>1</sup>	Refer to endocrine if osteoporosis T score $\geq 2.5$ DS or history of multiple fractures
Overweight Age 2–20 BMI >85–95th %tile Age >21 BMI 25–29.9 Obese Age 2–20 BMI $\geq 95$ th %tile Age >21 BMI >30			Height and weight BMI BP	Yearly	Fasting blood glucose Fasting serum insulin Fasting lipid profile	Every 2 years if overweight Every 5 years if normal weight	Evaluate for metabolic syndrome Refer to endocrine if hyperlipidemia or hyperglycemia
Metabolic syndrome			Height and weight BMI BP	Yearly	Fasting blood glucose Fasting serum insulin Fasting lipid profile	Every 5 years and prn	Refer to endocrine if insulin resistance/metabolic syndrome
Dyslipidemia					Fasting lipid profile	Baseline <sup>1</sup>	

<sup>1</sup> Baseline = Entry into long term follow-up program.

### *Growth Hormone Deficiency*

GH deficiency is the most common endocrine problem following cranial RT. Until growth is completed, the *COG LTFUG* recommend that children treated with cranial RT should undergo semi-annual screening for growth failure by assessing nutritional status, and monitoring of height, weight, and BMI percentiles, as well as sexual maturity rating. Additional considerations include bone age and thyroid studies for poorly growing children. Endocrine consultation should be obtained for children who are below the third percentile for height or weight, have dropped two percentile channels on the growth chart, or are growing slower than 4–5 cm per year. Endocrinology input should also be sought in adults considering GH replacement therapy. Bone mineral density assessment should be considered for children who are GH-deficient (table 3).

### *Precocious Puberty and Gonadotropin Deficiency*

Pubertal stage and maturation should also be assessed in survivors who have undergone cranial RT. True precocious puberty, early puberty, and normally-timed puberty with rapid progression have been associated with radiation doses of  $\geq 18$  Gy; female gender and younger age at

treatment are also risk factors [16, 17]. Radiation doses  $>40$  Gy may delay puberty through gonadotropin deficiency [10, 18]. The *COG LTFUG* screening recommendations include annual history (as appropriate) to include questions about pubertal onset and tempo, sexual function, menstrual and pregnancy history, Tanner staging and testicular volume assessment. Luteinizing hormone, follicle-stimulating hormone, and estradiol or testosterone should be obtained if precocious puberty is suspected in girls  $<8$  years and boys  $<9$ , as well as in all females at age 13 and all males at age 14 who are exposed to a therapy that could damage any part of the gonadal axis. Semen analysis could be obtained as requested by at-risk male patients. As has been demonstrated in populations without cancer, cigarette smoking can also adversely impact fertility.

Additional considerations include bone age and endocrine consultation if precocious puberty is suspected. Endocrine consultation should be obtained for suspected delayed puberty or gonadal failure. Consultation with a reproductive specialist may be necessary. Bone mineral density assessment should be obtained in patients with gonadotropin deficiency. In addition, counseling is critical to address the possibility of infertility and premature



**Table 4.** Health education materials available to patients and families at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org)

Endocrine-related health links	Relevant cancer therapy
Diet and physical activity	All survivors of pediatric cancer
GH deficiency	Total body irradiation, cranial radiation <sup>1</sup>
Central adrenal insufficiency	Cranial radiation <sup>1</sup>
Hyperprolactinemia	Cranial radiation <sup>1</sup>
Hypopituitarism	Total body irradiation, cranial radiation <sup>1</sup>
Thyroid problems	Total body irradiation, cranial radiation <sup>1</sup> , radiation that includes the thyroid <sup>2</sup>
Female health issues	Total body irradiation, cranial radiation <sup>1</sup> , gonadal radiation <sup>3</sup> , alkylating agents, heavy metals
Male health issues	Total body irradiation, cranial radiation <sup>1</sup> , gonadal radiation <sup>3</sup> , alkylating agents, heavy metals
Precocious puberty	Cranial radiation <sup>1</sup>
Bone health	Antimetabolites, corticosteroids, hematopoietic cell transplantation

<sup>1</sup> Cranial irradiation includes: cranial, orbital/eye, ear/infratemporal and nasopharyngeal.

<sup>2</sup> Thyroid irradiation includes: thyroid, neck, cervical spine, oropharyngeal, supraclavicular, mantle and mini mantle.

<sup>3</sup> Gonadal radiation includes: lumbosacral spine, abdomen and pelvis (females) and pelvis and testicular (males).

menopause, but at the same time the need for contraception, since recovery of fertility has been reported years after completion of cancer therapy.

#### *Central Hypothyroidism*

Central hypothyroidism in the setting of cranial RT is primarily the result of deficiencies of thyrotropin-releasing hormone (hypothalamic) and thyroid-stimulating hormone (pituitary) in children who have received >40 Gy of radiation [19, 20]. The *COG LTFUG* recommendations for annual screening include a focused history for symptoms of hypothyroidism, height, weight, skin, hair and thyroid examination, and a free T<sub>4</sub> and TSH. Additional considerations include referral to endocrinology for management of hypothyroidism, especially during pregnancy and if attempting to become pregnant.

#### *Central Adrenal Insufficiency*

Cranial RT may also give rise to central adrenal insufficiency. At radiation doses >40 Gy, the adrenal corticotropin hormone (ACTH) axis may be affected to varying degrees [21, 22]. The *COG LTFUG* recommend annual screening to include: a focused history with an assessment for failure to thrive, anorexia, dehydration, hypoglycemia, lethargy, and unexplained hypotension, and an 08:00 a.m. cortisol level. Because central adrenal insufficiency has been identified in survivors many years after the completion of therapy, an 08:00 a.m. serum cortisol level should be obtained yearly until 15 years off therapy [21, 23]. Additional considerations include a referral to endocrinology if morning cortisol levels are <10 µg/dl, for further evaluation and treatment.

#### *Hyperprolactinemia*

High-dose cranial RT (>40 Gy), mid-brain surgery, or tumor in the hypothalamic area may predispose a child to the development of hyperprolactinemia, which interferes with the pulsatile secretion of gonadotropin-releasing hormone [12, 24]. In the female, a history of galactorrhea and menstrual irregularities are of prime importance; in the male, the presence of galactorrhea and decreased libido warrant further evaluation. The *COG LTFUG* recommend a screening prolactin level in survivors with clinical signs and symptoms of prolactin excess. Additional considerations include imaging of the sella and referral to endocrine if the prolactin is elevated.

#### *Obesity/Metabolic Syndrome*

Cranial RT may also lead to weight management issues, often exacerbated by concurrent GH deficiency and hypothyroidism. Females, and children <4 years at the time of treatment, as well as those who have received hypothalamic radiation doses >18 Gy are at particular risk [25–27]. The *COG LTFUG* recommend annual assessment of blood pressure and body mass index. Fasting blood glucose, serum insulin, and lipid profile should be screened every 2 years in patients who are overweight or obese and every 5 years in normal weight patients. Additional considerations include the assessment of other co-morbid conditions including dyslipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, and insulin resistance. Nutrition, endocrinology, and/or cardiology referrals may be necessary for the management of dyslipidemia, hyperglycemia and hyperinsulinemia.

## Target-Organ Irradiation

Apart from cranial irradiation, target-organ irradiation involving the neck, abdomen, pelvis, and testes has the most pronounced endocrine late effects.

### *Thyroid Irradiation*

With radiation doses in excess of 10 Gy in the region of the thyroid, hypothyroidism or, rarely, hyperthyroidism may occur. Irradiation to the thyroid, especially at doses >25 Gy, may also predispose to the development of thyroid nodules; thus annual thyroid palpation is important during physical examination. Thyroid cancer may also develop after radiation to the neck. Recent evidence shows increasing risk with doses up to 30 Gy and then decreasing risk for thyroid cancer with higher doses of radiation [28]. The *COG LTFUG* recommend physical examination with particular attention to the thyroid gland, free T<sub>4</sub>, and TSH on an annual basis to screen for thyroid sequelae. Additional considerations include consultation with endocrinology for management of hypothyroidism, hyperthyroidism and evaluation of thyroid nodules/cancer for diagnostic biopsy, coordination of thyroidectomy, postoperative management, and radioablation, if indicated.

### *Gonadal Radiation*

Total body irradiation (TBI), abdominal, pelvic and lumbosacral spine radiation, especially in the postpubertal female, can compromise ovarian function. Mounting evidence suggests increased risk for premature menopause that must be factored into the long-term counseling of young adult survivors [29]. Women at highest risk include pubertal females treated with  $\geq 10$  Gy, and those who have received high doses of alkylating agents (see Chemotherapy section).

The testes are particularly sensitive to radiation, with germ cells suffering damage at much lower levels of radiation than Leydig cells [30–32]. The effect of testicular irradiation is highly dose-dependent. At doses of 1–3 Gy, azoospermia may be reversible; at 3–6 Gy, this reversibility is much less likely. Over 6 Gy, the patient is likely to suffer from permanent azoospermia. Doses >20 Gy may cause Leydig cell damage and affect production of testosterone. Please see the gonadal sections under cranial radiation for surveillance recommendations from the *COG LTFUG*.

## Total Body Irradiation

The effects of TBI parallel those of cranial and cranio-spinal RT, with added effects on specific endocrine end-organs. It is also important to note that TBI and HST are most often utilized as salvage therapy after primary cancer therapy failure; therefore, the cumulative effects of aggressive use of multiagent cancer therapy with multifactorial endocrine dysfunction should be considered. Endocrine complications reported following TBI include GH deficiency, primary hypothyroidism, thyroid nodules/cancer, and primary hypogonadism [13, 29, 33]. Survivors treated with TBI also manifest an increased risk of the metabolic syndrome, which may occur in the absence of overweight/obesity [34]. The *COG LTFUG* screening evaluations for each endocrine system and recommendations for referrals have been discussed previously and are summarized in table 3.

## Chemotherapy

Overall, the effects of chemotherapeutic agents on the endocrine system are less extensive than the effects of radiation. Nonetheless, the sequelae can be important and the *COG LTFUG* address the necessary screening. Gonadal dysfunction, dyslipidemia, and osteopenia/osteoporosis are the primary endocrine late effects observed following chemotherapy. We will address these in the context of each class of agent.

### *Gonadal Dysfunction*

Alkylating agents, heavy metals, and non-classical alkylators cause dose-related male and female gonadal dysfunction. Some alkylating agents, such as busulfan, procarbazine, and mechlorethamine, are particularly gonadotoxic [35]. Cyclophosphamide is one of the most commonly used alkylating agents in treatment protocols for pediatric cancers; men treated with cumulative doses of cyclophosphamide >7.5 g/m<sup>2</sup> are at highest risk of gonadal toxicity [36]. As with RT, germ cell function is impaired at lower doses than Leydig cell function [31, 37, 38]. In addition, the combination of chemotherapy with testicular, pelvic, or TBI significantly increases the risk of gonadal dysfunction [39]. Female gonadal dysfunction as a result of alkylating agents can result in delayed or arrested puberty, premature menopause, or infertility. High doses of alkylating agents, combinations of these agents, and combination with RT involving the neuroendocrine axis or ovarian region can all contribute to increased risk

of gonadal dysfunction [38, 39]. The *COG LTFUG* for screening for gonadal dysfunction and the additional considerations are as delineated above for gonadotropin deficiency following cranial radiation and are found in table 3.

#### *Low Bone Mineral Density*

Low bone mineral density is an adverse effect observed following the use of antimetabolite agents (particularly methotrexate) and corticosteroids (prednisone and dexamethasone). Altered bone metabolism caused by cancer treatment may hinder the acquisition of peak bone mass and increase the risk of premature onset and more severe osteopenia later in life. The World Health Organization defines osteopenia for adults as bone mineral density  $\geq 1$  and  $< 2.5$  T scores (the number of standard deviations from the mean) below the mean, and osteoporosis is defined as bone mineral density  $\geq 2.5$  T scores below the mean. Recommendations for children are extrapolated from the WHO definition and Z scores are calculated based on age and gender. The risk of decreased bone mineral density is increased when methotrexate is used in conjunction with corticosteroids, or when prolonged courses of corticosteroids are required, as in treatment for graft-versus-host disease. Patients with concomitant GH deficiency, hypogonadism, hyperthyroidism, or who have high-risk behaviors such as smoking, alcohol use, lack of weight-bearing exercise, or low calcium intake are at increased risk for low bone mineral density. The *COG LTFUG* recommends a screening bone mineral density evaluation by dual energy X-ray absorptiometry scan or quantitative computed tomography at 2 years after completion of cancer therapy in at-risk survivors. Additional considerations include: calcium and vitamin D supplementation, optimization of endocrine replacements and referrals for children with multiple fractures or a history of very low BMD. While it is recognized that there are no definitive standards for the referral or treatment of low bone mineral density in children, the prevalence and severity of bone mineral deficits observed in specific groups of childhood cancer survivors suggest that monitoring and providing interventions to correct bone mineral deficits may be beneficial [40, 41].

#### *Dyslipidemia*

The heavy metals carboplatin and cisplatin may cause dyslipidemia. High-risk patients include those with a family history of lipid disorders and those who are overweight or obese, a state which may be exacerbated by GH deficiency. The recommended screening by the *COG*

*LTFUG* involves a baseline fasting lipid profile. Additional considerations include counseling for dietary modification, exercise and weight loss. Pharmacologic interventions should be considered in patients unresponsive to dietary and lifestyle modifications [42, 43].

Thus far, it appears that antitumor antibiotics such as anthracyclines (examples include daunorubicin and doxorubicin), bleomycin and dactinomycin have no apparent endocrine late effects. The same is true of enzymes (asparaginase), plant alkaloids (vincristine and vinblastine), and epipodophyllotoxins (etoposide and teniposide).

### **Hematopoietic Cell Transplantation**

There is a growing body of research surrounding the late effects of stem cell transplantation [44]. A variety of endocrine late effects have been observed after transplant including gonadal dysfunction, poor growth, hypothyroidism and osteopenia/osteoporosis. These complications, which have been described above, arise primarily as a result of the preparatory regimen (high-dose chemotherapy and/or TBI) and may be exacerbated if primary therapy included cranial radiation, alkylating agent, steroid or antimetabolite chemotherapy [4, 45, 46]. The screening and criteria for referral to endocrinology are described above and are summarized in table 3.

### **Conclusion**

The timely and appropriate recognition of the endocrine sequelae of childhood cancer therapy can dramatically improve the quality of life of these survivors. Parents and patients should know they have access to the latest guidelines and health education materials at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org) (table 4). Certainly, many questions about the endocrine late effects of childhood cancer therapy remain unanswered. Recommendations are being made in 'real time' as we continue to learn more about the nature and impact of these sequelae. The *COG LTFUG* are a valuable tool for the screening and detection of endocrine problems among childhood cancer survivors. It is important for endocrinologists to understand the *COG* screening recommendations that are used for the early detection of endocrine sequelae and the rationale for pursuing further endocrine evaluation.



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